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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,437	12/21/2000	Bruce A. Hay	PC11862A	8404

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/07/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/747,437	Hay
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 23, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15, 17-20, and 22-27* is/are pending in the application.

4a) Of the above, claim(s) *5-10, 18-20, 22-24, 26, and 27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 11, 15, 17, and 25* is/are rejected.

7) ☒ Claim(s) *2-4 and 12-14* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 10 (filed 1/22/03), claims 15 and 17 have been amended, and claims 16 and 21 cancelled. Claims 1-15, 17-20 and 22-27 are pending. Claims 5-10, 18-20, 22-24, 26 27 remain withdrawn from consideration.

Applicants' arguments filed 1/22/03 have been considered and found persuasive in part. The (enablement) rejection of claims drawn to compounds *per se* is withdrawn; claims 15, 17 and 25 remain rejected.

*

The specification is objected to. In several of the chemical structures, hydrogen atoms are missing from the amide bonds and/or the indole nitrogen. See for example, page 7, page 20 (line 16+), page 21 (first structure) and pages 28, 29.

*

Claims 1 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending application Serial No. 09/618029. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A

timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 15 remains rejected because of the term "pharmaceutical carrier". This could be interpreted to mean that the carrier is itself a "pharmaceutical", or that the carrier is intended to be combined with a pharmaceutical. Either way, the claim implies an assertion of therapeutic efficacy, which is not in evidence. Claim 17 is rejected for each of three separate reasons: (a) claim 17 recites the term "pharmaceutical composition"; (b) claim 17 recites the term "pharmaceutical carrier"; and (c) claim 17 recites the term "effective amount". The following is suggested in the case of claim 17:

> *A composition comprising a pharmaceutically acceptable carrier in combination with a compound according to claim 1 in an amount effective to inhibit binding of somatostatin to a type 2 somatostatin receptor.*

Claim 25 is rejected because of its recitation of the term "pharmaceutical carrier". It is suggested that the term "pharmaceutical" be deleted from claim 25.

Applicants have argued that the specification discloses that somatostain is "involved" in "various metabolic processes". The examiner does not dispute that somatostain is "involved" in "various metabolic processes". However, the claims are not drawn to a method of becoming involved in unspecified metabolic processes; rather, the claims at issue are drawn to "pharmaceutical compositions". The term "pharmaceutical" is an intended use limitation which conveys an intent to use the compounds to treat human disease. It is asserted in the specification that the claimed compounds can be used to treat frailty and hypoglycemia. It is also asserted that the claimed compounds can somehow "improve" the function of unspecified organs in patients with unspecified diseases. Perhaps this would include inducing repair of liver tissue in patients afflicted with hepatitis or inducing repair of pancreatic tissue in subjects afflicted with pancreatic cancer. Or perhaps the term at issue is intented to encompass the successful therapy of kidney failure. Applicants' intent in this regard is not made clear; one can only speculate. It is also asserted in the specification that the claimed compounds can be used to treat immunodeficiency disorders; this would, of course, include HIV and AIDS. It is also asserted in the specification that the claimed compounds can be used to accelerate skeletal growth, and that the claimed compounds will be effective to eliminate wrinkles from skin. Regardless of how the

claimed compounds may be "involved" in "metabolic processes", it is not made clear even what the connection between the cited disorders and sst2 antagonism.

Applicants have argued that the specification defines the structures of the claimed compounds, and lists species. Whether the specification has listed 10 species or 10 million makes no difference with respect to the matter of enablement. Applicants have pointed out that the specification provides suggestions for how to combine the claimed compounds with conventionally used pharmaceutically acceptable carriers. In response, the examiner would point out that virtually any organic compound can be combined with a pharmaceutically acceptable carrier, but that the mere act of combining does not confer pharmacological activity upon an otherwise inactive compound. For example, suppose that a chemist were to formulate benzoic acid (4% by weight) into a gelatin tablet, and that the chemist were to then assert that by ingesting four of these tablets per day for 200 days, that tumor volumes (in a cancer patient) would be significantly reduced. Would applicants find this convincing? Next, applicants have made the following arguments:

(a) the examiner should not reject the claims on the basis that the specification fails to teach how to make the compounds;

(b) a rejection under 35 USC §101 should not be imposed, and

(c) the examiner should not have imposed a scope rejection.

As it happens, all three of these premises are invalid, i.e., (a) the examiner has not argued that "undue experimentation" would be required to synthesize any one of the claimed

compounds; (b) a rejection under 35 USC §101 has not been imposed, and (c) the examiner has not imposed a scope rejection. With respect to the last point, applicants have begun with the premise that within the claimed genus, there surely must be at least a few compounds that can be used to treat one of the human diseases recited above. After having set forth this premise, applicants have gone on to argue that the full genus is enabled, even if there may be a few compounds within that genus which are not effective to treat the cited diseases. While issues of enablement and scope may be related to one another, an enablement rejection can be entirely proper in the absence of an allegation of excessive scope; similarly, a scope rejection can be entirely proper in the absence of an allegation of insufficient enablement for at least one of the claimed embodiments. Thus, applicants have hypothesized the existence of various rejections which were never imposed. Accordingly, there is no need to debate the merits of hypothetical rejections that have not been imposed.

Absent from applicants' arguments is any discussion of the issue at hand, which is that of therapeutic efficacy of the claimed compositions. The issue is that of whether one can "predict" the therapeutic efficacy of a compound which has been shown to antagonize sst2 in *vitro*. The examiner maintains that such a prediction cannot be made reliably. Should applicants choose to continue the discussion, it is suggested that applicants address this specific issue.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an <u>increase</u>

in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In addition to the foregoing, Hocart (*J Med Chem* **41**, 1146, 1998) discloses (e.g., table 3) that very minor changes in structure can eliminate sst2 antagonistic activity. The assertion by the examiner is not that the claimed compounds will fail to antagonize sst2 *in vitro*, or even *in vivo*. The first point to be made regarding Hocart is that receptor antagonism is a question of degree. At some point in the future, applicants may provide a copy of an article which shows that there exists a compound which not only antagonzied sst2 in vitro, but could also increase blood glucose levels in hypoglycemic rats. No such article has been identified by applicants as of yet, but this may happen at some point in the future. Should that event come to pass, one of the arguments will be to reiterate the point that receptor antagonism is a question of degree, and that even if a highly potent (prior art) antagonist of sst2 is effective to raise blood glucose levels in hypoglycemic rats, it does not

follow therefrom that much weaker antagonists (as claimed) will be similarly effective. There are other arguments as well, including the fact that if two compounds are equally potent in an *in vitro* receptor antagonism assay, it is not infrequently the case that one such compound exhibits a measurable physiological response, while the other does not. However, at the present time, applicants have not even established that the "state of the art" is such that one can expect therapeutic efficacy from sst2 antagonists. This, coupled with the lack of working examples (establishing therapeutic efficacy) and the unpredictability in the art of receptor antagonism leads one to a conclusion that "undue experimentation" would be required to practice the claimed invention. It is suggested that the term "pharmaceutical" be eliminated from the claims (although no objection would be raised to the term *pharmaceutically acceptable* carrier), and that claim 17 be amended to make it clear what the objective of the "effective amount" might be.

*

Claims 17 and 25 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 17 is indefinite as to the objective of the "effective amount".
- Claim 25 requires components that are not required by claim 15. Accordingly, the scope of claim 15 should be expanded to encompass the possibility of GHRP or

GHRH being present, or else claim 25 should be made dependent on claim 1.

✺

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800